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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
20-430/S-003**

**Clinical Pharmacology and Biopharmaceutics
Review**

Investigational New Drug Application Clinical Pharmacology and Biopharmaceutics Review

IND/NDA:	20-430
Submission(s):	Type: Geriatric labeling supplement Suppl.: SE8-003 Letter Date: 8/25/00 Date Received: 8/28/00
Reviewer:	Sandip K. Roy, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
Clinical Division:	Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Drug:	
Generic Name:	Danaparoid sodium
Other Name(s):	
Trade Name:	Orgaran Injection
Molecular Weight:	5500 Daltons
Molecular Formula:	84% Heparan sulfate, 12% Dermatan sulfate, 4% Chondroitin sulfate
Relevant IND(s)/NDA(s):	
Drug Class:	Anticoagulant (glycosaminoglycuronan antithrombotic agent)
Dosage Form:	Injection
Route of Administration:	Subcutaneous
Dosing Regimen:	1 – 4 hrs pre-operatively, and then not sooner than 2 hrs after surgery continued throughout the period of post-operative care until risk of deep vein thrombosis has diminished
Sponsor:	Organon Inc., West Orange, NJ 07052
Proposed Indication:	Prophylaxis of post-operative deep venous thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery

SYNOPSIS

This submission provides for geriatric labeling supplement to approved NDA 20-430 under geriatric labeling regulation [21 CFR 201.57 (f) (10)]. Following table shows that overall 44 patients (55 – 76 years of age) participated in the four clinical studies that were submitted in the original NDA in support of the approved indication for Orgaran. These studies however, did not include sufficient numbers of patients to determine whether patients ≥ 65 yrs respond differently than patients < 65 yrs.

Study Number ^a (Location of report in NDA 20-430)	Number of patients and sex (Age range [Mean])
82049 (Vol. 2.165)	4 F (58-67 [62])
84006/84007 (Vol. 2.162)	4 F (28-33 [31]) 4 F, 4 M (56-65 [61] ^b)
84021 (Vol. 2.161)	10 F, 10 M (56-76 [68])
85014 (Vol. 2.130, 2.131, and 2.132)	6 F, 6 M (55-68 [58])
Totals	4 F (28-33 [NA]) 24 F, 20 M (55-76 [NA])

Source data: Table 1 from the Integrated Summary of Safety, NDA 20-430, Volume 2.255, pages 85, 90, 92; Table 1 of Clinical Study Report 84006/84007; NDA 20-430, Vol. 2.162, page 19.

Note: F = female; M = male; NA = data not available

^a All were non-US studies.

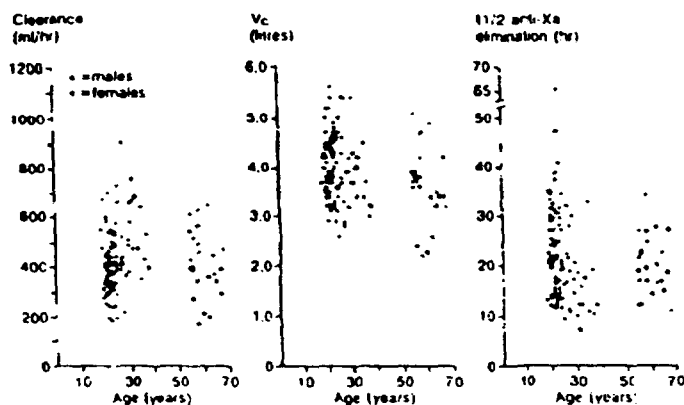
^b Calculated from individual subject data

Appendix I

• Pharmacokinetic Considerations on Orgaran (Org 10172) Therapy

Danhof, M, de Boer A, Magnani, HN, Stiekema, JCJ
Haemostasis 1992;22:73 – 84

In order to determine the influence of age on the pharmacokinetics of Orgaran, the combined data of several investigations were analyzed. The results were presented as scatterplots of the pharmacokinetic parameter of anti-Xa activity vs age (up to 70 yrs). As shown in the figure below no clear relationship was observed between age and the pharmacokinetic parameters of anti-Xa activity.



No details about the source of this data or the study design were provided for these studies.

In addition, in a population pharmacokinetic analysis reported in the Human pharmacokinetics and Bioavailability section of original NDA, the covariates of age, sex, and weight were not found to be important for Orgaran. In one of the articles [Appendix I – Danhof *et al.*, Haemostasis, 1992, 22(2):73 – 84] submitted by the sponsor the authors concluded that there was no clear relationship between age and the clearance, volume of the central compartment, or elimination half-life of the anti-Xa activity. Another article [Appendix II – Stiekema *et al.*, Br J Clin Pharmacol 1989, 27(1): 39 – 48] compared half-life of elimination of Orgaran anti-Xa activity in volunteers of 55 to 68 yrs age to that found in young volunteers in a previously conducted study. No data was collected on young volunteers in this study. Based on these results we agree with the sponsor that no meaningful conclusions can be drawn with respect to differences in the pharmacokinetics of Orgaran in patients ≥ 65 yrs versus patients < 65 yrs.

RECOMMENDATION

This supplement is approvable from the OCPB perspective.



Sandip K. Roy, Ph.D.
Clinical Pharmacologist

6/18/2001

Date

FT initiated by Suresh Doddapaneni, Ph.D.

c.c. /NDA 20-430
/HFD-180 (Division files, KOliver)
/HFD-870 (SDoddapaneni, HMalinowski, SRoy)
/CDR (ZZadeng)

Appendix II

Safety and pharmacokinetics of the low molecular weight heparinoid Org 10172 administered to healthy elderly volunteers

**Stiekema, JCJ, Wijnand, HP, Van Dinther, THG, Moelker, HCT, Dawes, J, Vincenzo, A, Toeberich, H
Br. J. Clin. Pharmacol. (1989), 27, 39 – 48**

- ◆ In an open randomized balanced cross-over study each of the 12 elderly volunteers (6 male and 6 female) received one single IV injection of Orgaran in one treatment period and two simultaneously administered SC injections of Orgaran in other treatment period. The two treatments were separated by a washout period of at least 1 week.
- ◆ The absolute bioavailability, as measured by plasma anti-Xa activity, approached 100% in both sexes.
- ◆ The half-life of elimination of anti-Xa activity was 19.2 ± 6.1 hr, which is similar to that found previously in young volunteers